Predicting acute myocardial infarction with a single blood draw

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Abstract: BACKGROUND: We desired to determine cardiac troponin (cTn) concentrations necessary to achieve a positive predictive value (PPV) of 75% for acute myocardial infarction (AMI) to justify immediate admission of patients to a monitored unit and, in general, early coronary angiography. METHODS: In a prospective multicenter diagnostic study enrolling patients presenting to the emergency department with symptoms suggestive of AMI, final diagnoses were adjudicated by 2 independent cardiologists based on clinical information including cardiac imaging. cTn concentrations were measured using 5 different sensitive and high-sensitivity cTn (hs-cTn) assays in a blinded fashion at presentation and serially thereafter. The diagnostic end point was PPV for rule-in of AMI of initial cTn concentrations alone and in combination with early changes. RESULTS: Among 3828 patients, 616 (16%) had an AMI. At presentation, 7% to 14% of patients had cTnT/I concentrations associated with a PPV of 75%. Adding absolute or relative changes did not significantly further increase the PPV. PPVs increased from 46.5% (95% CI, 43.6-49.4) for hs-cTnT at presentation >14 ng/L to 78.9% (95% CI, 74.7-82.5) for >52 ng/L ($P < 0.001$), whereas PPVs in higher hs-cTnT strata remained largely unchanged [e.g., 82.4% (95% CI, 77.5-86.7) for >80 ng/L vs 83.9% (95% CI, 76.0-90.1) for >200 ng/L ($P = 0.72$)]. The addition of early changes in hs-cTnT further increased the PPV up to 60 ng/L, but not for higher concentrations. CONCLUSIONS: Serial sampling does not seem necessary for predicting AMI and concurrent decision-making in about 10% of patients, as it only marginally increases the PPV for AMI and not in a statistically or clinically significant way. CLINICALTRIALSGOV IDENTIFIER: NCT00470587.

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Predicting Acute Myocardial Infarction with a Single Blood Draw

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BACKGROUND: We desired to determine cardiac troponin (cTn) concentrations necessary to achieve a positive predictive value (PPV) of ≥75% for acute myocardial infarction (AMI) to justify immediate admission of patients to a monitored unit and, in general, early coronary angiography.

METHODS: In a prospective multicenter diagnostic study enrolling patients presenting to the emergency department with symptoms suggestive of AMI, final diagnoses were adjudicated by 2 independent cardiologists based on clinical information including cardiac imaging. cTn concentrations were measured using 5 different sensitive and high-sensitivity cTn (hs-cTn) assays in a blinded fashion at presentation and serially thereafter. The diagnostic end point was PPV for rule-in of AMI of initial cTn concentrations alone and in combination with early changes.

RESULTS: Among 3828 patients, 616 (16%) had an AMI. At presentation, 7% to 14% of patients had cTnT/I concentrations associated with a PPV of ≥75%. Adding absolute or relative changes did not significantly further increase the PPV. PPVs increased from 46.5% (95% CI, 43.6–49.4) for hs-cTnT at presentation >14 ng/L to 78.9% (95% CI, 74.7–82.5) for >52 ng/L ($P < 0.001$), whereas PPVs in higher hs-cTnT strata remained largely unchanged [e.g., 82.4% (95% CI, 77.5–86.7) for >80 ng/L vs 83.9% (95% CI, 76.0–90.1) for >200 ng/L ($P = 0.72$)]. The addition of early changes in hs-cTnT further increased the PPV up to 60 ng/L, but not for higher concentrations.

CONCLUSIONS: Serial sampling does not seem necessary for predicting AMI and concurrent decision-making in about 10% of patients, as it only marginally increases the PPV for AMI and not in a statistically or clinically significant way.

ClinicalTrials.gov Identifier: NCT00470587.

Patients with symptoms suggestive of an acute myocardial infarction (AMI)[9] such as chest discomfort or angina pectoris account for up to 10% of all emergency department (ED) presentations *(1)*. Immediate identification of AMI as a life-threatening disorder is critical for the early initiation of an appropriate evidence-based therapy. For the safe and rapid rule-out or rule-in of AMI, electrocardiography (ECG) and cardiac troponin (cTn) complement clinical assessment and form the 3 essential diagnostic cornerstones *(2, 3)*.

The introduction of sensitive cardiac troponin (s-cTn) and high-sensitivity cardiac troponin (hs-cTn) assays enabled the precise measurement of cTn concentrations around the 99th percentile and even in the reference interval *(4, 5)*, and thereby substantially improved the diagnostic accuracy for AMI at presentation *(6, 7)*. However, the clinical introduction of hs-cTn assays also led to substantial uncertainty among clinicians on how to best use them *(1–3)*. According to current recommendations, hs-cTn concentrations should be interpreted quantitatively with higher concentrations indicating a higher like-

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[9] Nonstandard abbreviations: AMI, acute myocardial infarction; ED, emergency department; ECG, electrocardiography; cTn, cardiac troponin; s-cTn, sensitive cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; PPV, positive predictive value; APACE, Advantageous Predictors of Acute Coronary Syndrome Evaluation.

lihood for the presence of AMI *(1–3)*. Although guidelines recommend the use of 2 measurements of cTn in the early diagnosis of AMI to quantify early hs-cTn changes, a recent pilot study questioned the general need for serial sampling for rule-in of AMI *(8)*.

Because the concept of rapid rule-in of AMI based on a single measurement of cTn has enormous medical and economic appeal *(1–3)*, we aimed to determine the cTn concentrations necessary to achieve a positive predictive value (PPV) of ≥75% for AMI using 5 different s-cTn and hs-cTn assays in a large multicenter diagnostic study. Such threshold concentrations could be applied to justify immediate admission to a monitored unit and, in general, early coronary angiography.

Materials and Methods

STUDY DESIGN AND POPULATION

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study with 12 centers in 5 European countries aiming to advance the early diagnosis of AMI (ClinicalTrials.gov registry, number NCT00470587) *(6, 9–16)*.

Adult patients presenting to the ED with symptoms suggestive of AMI (such as acute chest discomfort and angina pectoris) with an onset or peak within the past 12 h were recruited. Although enrollment was irrespective of renal function, patients with terminal kidney failure on chronic dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

For this analysis, patients were excluded if they had ST-segment elevation myocardial infarction or an unknown diagnosis after adjudication and at least 1 increased hs-cTnT concentration possibly indicating AMI (for whom 3 independent cardiologists were not able to make a final diagnosis).

The authors designed the study, gathered and analyzed the data according to the STARD guidelines for studies of diagnostic accuracy (see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue3), vouched for the data and analysis, wrote the paper, and decided to publish.

ROUTINE CLINICAL ASSESSMENT

Patients underwent clinical assessment that included medical history, physical examination, standard blood test including serial measurements of local hs-cTn, 12-lead ECG, chest radiography, continuous ECG rhythm monitoring, and pulse oximetry. Treatment of patients was left to the discretion of the attending physician.

ADJUDICATED FINAL DIAGNOSIS

Adjudication of the final diagnosis was performed by 2 independent cardiologists at the core laboratory (University Hospital Basel) applying the universal definition of AMI using 2 sets of data: first, all available medical records obtained during clinical care including history, physical examination, results of laboratory testing including serial clinical hs-cTn determinations, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in coronary angiography pertaining to the patient from the time of ED presentation to 90-day follow-up evaluation; second, study-specific assessments including detailed chest pain characteristics using 34 predefined criteria, serial hs-cTnT blood concentrations obtained from study samples, and clinical follow-up by telephone and/or mail. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. To address the uncommon, but previously described, phenomenon of discrepant results for hs-cTnT and hs-cTnI, we performed a second adjudication using serial hs-cTnI (rather than hs-cTnT) blood concentrations from study samples.

It needs to be highlighted that patients' care at all participating study sites was left to the discretion of the attending physicians and that serial sampling of study-specific hs-cTn concentrations was independent from local triage protocols and time points of blood draws for local cTn measurements (e.g., at study sites using a 0/6-h protocol, samples were taken locally at 0 h and 6 h and at 1 h, 2 h, and 3 h for study purposes only).

AMI was defined and hs-cTn interpreted as recommended in the current guidelines *(17–19)*. In brief, myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 cTn value above the 99th percentile, together with a significant rise and/or fall. The criteria used to define a rise and/or fall in conventional cTn and hs-cTnT are described in detail in the Methods section found in the online Data Supplement. All other patients were classified in the categories of unstable angina, noncardiac chest pain, cardiac but noncoronary disease (e.g., tachyarrhythmias, perimyocarditis), and symptoms of unknown origin with normal concentrations of hs-cTnT.

INVESTIGATIONAL hs-cTn MEASUREMENTS

Blood samples for determination of hs-cTnT and the other (h)s-cTn assays were collected into tubes containing potassium EDTA or serum, respectively. Additional samples were collected at 1 h, 2 h, and 3 h after presentation. Serial sampling was discontinued when a patient was released or transferred to the catheter laboratory for acute treatment. After centrifugation, samples were fro-

zen at −80 °C until assayed in a blinded fashion at a dedicated core laboratory.

The hs-cTnT assay (Elecsys 2010, Roche Diagnostics) has a 99th percentile concentration of 14 ng/L with a corresponding CV of 10% at 13 ng/L *(4)*. The limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, respectively *(4)*. None of the hs-cTnT measurements in this analysis were affected by the 2010 to 2012 calibration shift *(20, 21)*. Estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula *(22)*. Investigational (h)s-cTn measurements using the other 4 assays can be found in the Methods section of the online Data Supplement.

FOLLOW-UP AND CLINICAL END POINTS

Patients were contacted 3, 12, and 24 months after discharge by telephone calls or in written form. Additionally, information regarding death during the follow-up period was obtained from the patient's hospital notes, the family physician's records, and the national registry on mortality. The primary outcome measure was prediction of AMI as quantified by the resulting PPVs.

STATISTICAL ANALYSIS

Continuous variables are represented as median values with interquartile range, categorical variables by numbers, and percentages. Differences in PPVs were assessed using the Pearson χ^2 test.

As an example, for hs-cTnT we stratified patients according to concentrations at presentation of ≤14 ng/L, >14 ng/L, >30 ng/L, >52 ng/L, >60 ng/L, >80 ng/L, >100 ng/L, >200 ng/L, and >400 ng/L. Sensitivity analyses were performed to assess the diagnostic performance of (h)s-cTn by resulting sensitivities, negative predictive values, specificities, PPV, and diagnostic odds ratios for the respective (h)s-cTn cutoffs alone and in combination with early absolute and relative changes within 1 h, 2 h, and 3 h. Relative changes were defined consistently throughout all assays as a change in cTn concentrations of ≥10% within 1 h and ≥20% within 2 h or 3 h. Absolute changes were assay-specific as described previously, e.g., ≥5 ng/L within 1 h and ≥10 ng/L within 2 h or 3 h for hs-cTnT by the Elecsys *(16, 23, 24)* (see the online Data Supplement). Patients with highly increased cTn concentrations at presentation but final diagnoses other than AMI were further investigated. Subgroup analyses were performed in patients with type 1 myocardial infarction only (instead of type 1 and type 2 myocardial infarction) and in patients with ST-depression and/or T-wave inversions in the ECG.

We did not adjust for multiple testing. To minimize the risk of false-positive findings ($P < 0.05$ for differences in PPV despite no real difference for 1 assay at 1 time point), we have prioritized the analysis for hs-cTnT, as this is the largest data set available in APACE (primary analysis) and because hs-cTnT is the only hs-cTn assay currently approved for clinical use in the US by the Food and Drug Administration *(1)*. The analyses with the 4 other (h)s-cTnI assays were performed to investigate whether the findings for hs-cTnT are generalizable to the other (h)s-cTn assays.

All hypothesis testing was 2-tailed, and P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows (version 24.0, SPSS), R (version 3.3.1, "epiR 0.9.79"), and MedCalc (version 9.6.4.0, MedCalc Software).

Results

CHARACTERISTICS OF PATIENTS

From April 2006 to August 2015, a total of 3828 patients were eligible for the analyses for hs-cTnT and 3548 for hs-cTnI (see Fig. 1 in the online Data Supplement). Patients with highly increased hs-cTnT or hs-cTnI concentrations at presentation more often had ECG changes such as ST-segment depressions or T-wave inversions and higher rates of coronary angiography and percutaneous coronary interventions (Table 1; see also Table 2 in the online Data Supplement). Similar findings emerged using the 4 (h)s-cTnI assays (see Tables 3–5 in the online Data Supplement).

ADJUDICATED FINAL DIAGNOSIS

The adjudicated final diagnosis was AMI in 616 of 3828 patients (16%), unstable angina in 364 of 3828 (9%), cardiac symptoms of origin other than coronary artery disease such as tachyarrhythmias, takotsubo cardiomyopathy, heart failure, or myocarditis in 565 of 3828 (15%), noncardiac symptoms in 2125 of 3828 (56%), and unknown in 158 of 3828 patients (4%). The proportion of patients with AMI increased with higher hs-cTnT concentrations at presentation (Fig. 1A). Similar findings emerged using the 4 (h)s-cTnI assays (Fig. 1B; see also Figs. 2–4 in the online Data Supplement). Non-hs-cTn assays were used in 1860 of 3828 (49%) patients and hs-cTn assays were used in 1968 of 3828 (51%) patients for clinical care at different study sites.

AVAILABLE SAMPLES AT EACH TIME POINT

For hs-cTnT (Elecsys), 3828 patients had available 0-h samples, 3123 of 3828 patients (82%) had available 1-h samples, 2586 of 3828 patients (68%) had available 2-h samples, and 1508 of 3828 patients (39%) had available 3-h samples.

For hs-cTnI (Architect), 3548 patients had available 0-h samples, 2828 of 3548 patients (80%) had available 1-h samples, 2272 of 3548 patients (64%) had available 2-h samples, and 1153 of 3548 patients (32%) had available 3-h samples. Numbers of available samples

Table 1. Baseline characteristics of the patients stratified according to hs-cTnT concentrations at presentation.

Baseline characteristics	≤14 ng/L (n = 2635)		>14 ng/L (n = 1193)		>30 ng/L (n = 641)		>52 ng/L (n = 417)		>60 ng/L (n = 371)		>80 ng/L (n = 290)		>100 ng/L (n = 234)		>200 ng/L (n = 118)		>400 ng/L (n = 57)	
Age in years, median (IQR[a])	56	45–67	74	63–81	74	61–81	73	60–80	73	59–80	73	59–80	73	58–80	73	59–82	75	59–82
Male, sex, n (%)	1737	66%	846	71%	465	73%	299	72%	265	71%	207	71%	169	72%	84	71%	42	74%
Risk factors, n (%)																		
Hypertension	1383	53%	966	81%	502	78%	319	77%	276	74%	212	73%	174	74%	85	72%	43	75%
Hypercholesterolemia	1115	42%	753	63%	394	62%	255	61%	220	59%	173	60%	141	60%	67	57%	36	63%
Diabetes	350	13%	306	26%	168	27%	98	24%	80	22%	54	19%	44	19%	18	15%	7	13%
Current smoking	760	29%	207	17%	135	21%	87	21%	81	22%	65	23%	56	24%	31	27%	15	27%
History of smoking	882	34%	528	44%	286	45%	181	44%	152	41%	116	40%	90	39%	42	36%	22	39%
BMI, kg/m^2, median (IQR)	26	24–30	27	24–30	26	24–29	26	24–29	26	24–29	26	24–29	26	24–29	26	23–29	26	24–30
Medical history, n (%)																		
Coronary artery disease	699	27%	579	49%	294	46%	174	42%	149	40%	115	40%	91	39%	40	34%	19	33%
Previous myocardial infarction	490	19%	411	35%	212	33%	127	31%	108	29%	82	28%	63	27%	28	24%	15	26%
Previous revascularization	606	23%	444	37%	217	34%	129	31%	111	30%	82	28%	64	27%	26	22%	11	19%
Peripheral artery disease	77	2.9%	135	11%	91	14%	48	12%	36	9.7%	28	9.7%	21	9.0%	13	11%	7	12%
Previous stroke	98	3.7%	109	9.1%	59	9.2%	41	10%	36	9.7%	27	9.3%	20	8.5%	15	13%	10	18%
Positive family history	476	18%	78	6.5%	52	8.1%	36	8.6%	35	9.4%	25	8.6%	20	8.5%	9	7.6%	7	12%
Biochemistry, median (IQR)																		
Hemoglobin, mg/L	145	135–154	138	123–150	137	122–151	139	122–152	140	125–153	140	125–153	142	126–154	141	126–154	140	125–151
Creatinine clearance, mL/min/m^2	90	77–104	70	52–87	70	49–89	71	50–90	73	53–91	74	55–94	74	56–94	76	60–95	69	50–92
ECG findings, n (%)																		
ST-segment depression	133	5.1%	270	23%	187	30%	134	33%	122	34%	95	34%	79	35%	34	30%	23	41%
Left bundle branch block	50	1.9%	85	7.3%	47	7.5%	36	8.8%	31	8.5%	26	9.2%	18	7.9%	8	7.0%	6	11%
T-wave inversion	193	7.3%	244	21%	143	22%	106	25%	95	26%	76	26%	61	26%	35	30%	16	28%
No significant ECG changes	2213	84%	663	56%	306	48%	177	42%	156	42%	117	40%	93	40%	44	37%	15	26%
Procedures within 30 days after index admission, n (%)																		
Coronary angiography	324	12%	574	48%	400	62%	290	70%	263	71%	217	75%	183	78%	91	77%	44	77%
Percutaneous coronary intervention	152	5.8%	346	29%	248	39%	178	43%	161	43%	131	45%	110	47%	59	50%	30	53%
CABG	22	0.8%	55	4.6%	44	6.9%	32	7.7%	30	8.1%	24	8.3%	22	9.4%	8	6.8%	6	11%
Ergometry	659	25%	236	20%	103	16%	63	15%	52	14%	36	12%	28	12%	15	13%	6	11%
Myocardial perfusion scanning	257	9.8%	132	11%	51	8.0%	27	6.5%	20	5.4%	14	4.8%	11	4.7%	5	4.2%	2	3.5%

[a] IQR, interquartile range; BMI, body mass index; ECG, electrocardiogram; CABG, coronary artery bypass grafting.

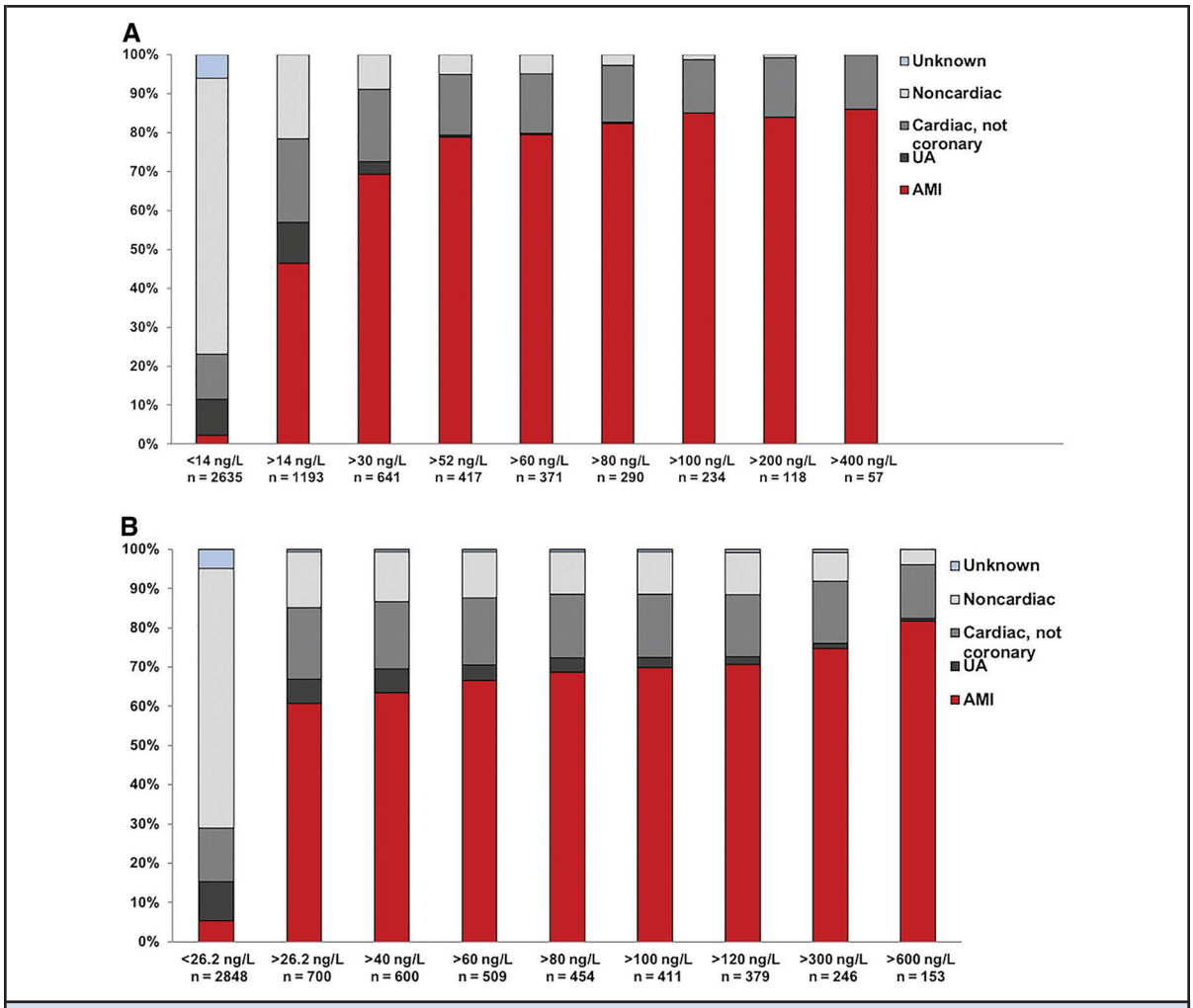

Fig. 1. Final diagnoses according to hs-cTn concentrations at presentation.
(A), hs-cTnT; (B), hs-cTnI (Architect). UA, unstable angina.

for the other 3 (h)s-cTnI assays are given in the online Data Supplement. Missing cTn concentrations taken as part of the study at 1 h, 2 h, and 3 h can be explained as a result of logistics issues in the EDs and/or diagnostic procedures performed around the 1-h to 3-h windows.

DIAGNOSTIC PERFORMANCE OF DIFFERENT hs-cTnT CONCENTRATIONS AT PRESENTATION

The resulting PPVs for prediction of AMI increased from 46.5% (95% CI, 43.6–49.4) for hs-cTnT >14 ng/L to 78.9% (95% CI, 74.7–82.5) for >52 ng/L ($P < 0.001$), whereas PPVs in higher hs-cTnT strata remained largely unchanged (Table 2). Similar findings emerged using the 4 (h)s-cTnI assays (see Tables 6–9 in the online Data Supplement). Assay-specific cutoffs to achieve predefined PPVs of 70% and 75% or greater were highly variable among 4 different cTnI assays, and in general at least twice as high as the necessary cTnT concentration (Table 3).

DIAGNOSTIC PERFORMANCE OF DIFFERENT (h)s-cTn CONCENTRATIONS AT PRESENTATION ACCORDING TO THE SECONDARY ADJUDICATION INCLUDING hs-cTnI (ARCHITECT)

Using the secondary adjudication, PPVs for the (h)s-cTnI assays were higher compared with the primary adjudication. However, findings regarding the additional value of early changes remained unchanged (see Tables 10–13 in the online Data Supplement).

DIAGNOSTIC PERFORMANCE OF EARLY ABSOLUTE AND RELATIVE hs-cTnT CHANGES IN ADDITION TO hs-cTnT CONCENTRATIONS AT PRESENTATION

Addition of early changes in hs-cTnT further increased the PPV for AMI up to an initial hs-cTnT concentra-

Table 2. Performance of different cutoffs of hs-cTnT for prediction of AMI.[a]

	Sensitivity (95% CI)	Specificity (95% CI)	NPV[b] (95% CI)	PPV (95% CI)	Diagnostic odds ratio (95% CI)
hs-cTnT baseline >14 ng/L (n = 1193)	90.1% (87.4–92.4)	80.1% (78.7–81.6)	97.7% (97.0–98.3)	46.5% (43.6–49.4)	36.7 (27.7–48.5)
+ Absolute change (1 h, ≥5 ng/L) (n = 373/1193, 31%)	60.6% (56.1–64.9)	97.9% (97.3–98.4)	93.8% (92.9–94.7)	82.3% (78.0–86.1)	70.7 (52.2–95.6)
+ Absolute change (2 h, ≥10 ng/L) (n = 245/1193, 21%)	53.7% (48.6–58.8)	98.8% (98.3–99.2)	94.4% (93.4–95.2)	84.9% (79.7–89.2)	93.9 (64.1–137.5)
+ Absolute change (3 h, ≥10 ng/L) (n = 167/1193, 14%)	53.6% (47.3–59.8)	99.1% (98.7–99.5)	95.9% (95.0–96.6)	85.0% (78.6–90.1)	131.2 (82.6–208.3)
+ Relative change (1 h, ≥10%) (n = 365/1193, 31%)	51.7% (47.2–56.2)	96.7% (95.9–97.3)	92.5% (91.4–93.4)	71.8% (66.8–76.4)	31.2 (23.9–40.6)
+ Relative change (2 h, ≥20%) (n = 232/1193, 19%)	46.8% (41.7–51.9)	98.3% (97.7–98.8)	93.5% (92.6–94.4)	78.0% (72.1–83.2)	51.3 (36.4–72.2)
+ Relative change (3 h, ≥20%) (n = 177/1193, 15%)	50.6% (44.3–56.8)	98.5% (97.9–99.0)	95.6% (94.7–96.3)	75.7% (68.7–81.9)	67.2 (45.6–98.8)
hs-cTnT baseline >30 ng/L (n = 641)	72.2% (68.5–75.8)	93.9% (93.0–94.8)	94.6% (93.7–95.4)	69.4% (65.6–73.0)	40.0 (31.8–50.3)
+ Absolute change (1 h, ≥5 ng/L) (n = 307/641, 48%)	50.0% (45.6–54.4)	98.5% (98.0–99.0)	92.3% (91.3–93.2)	84.7% (80.1–88.6)	66.5 (47.5–93.0)
+ Absolute change (2 h, ≥10 ng/L) (n = 206/641, 32%)	41.8% (36.9–46.7)	99.0% (98.6–99.4)	92.7% (91.8–93.6)	85.0% (79.3–89.6)	72.2 (48.1–108.1)
+ Absolute change (3 h, ≥10 ng/L) (n = 132/641, 21%)	35.1% (29.9–40.5)	99.5% (99.1–99.7)	93.5% (92.6–94.4)	87.1% (80.1–92.4)	97.7 (57.6–165.7)
+ Relative change (1 h, ≥10%) (n = 226/641, 35%)	37.3% (33.1–41.7)	99.0% (98.5–99.4)	90.6% (89.5–91.6)	85.8% (80.6–90.2)	58.4 (39.4–86.4)
+ Relative change (2 h, ≥20%) (n = 152/641, 24%)	30.8% (26.3–35.5)	99.3% (98.9–99.6)	91.5% (90.5–92.5)	84.9% (78.1–90.2)	60.5 (38.1–95.8)
+ Relative change (3 h, ≥20%) (n = 109/641, 17%)	29.3% (24.3–34.6)	99.6% (99.2–99.8)	93.0% (92.0–93.9)	88.1% (80.4–93.5)	98.1 (54.1–177.7)
hs-cTnT baseline >52 ng/L (n = 417)	53.4% (49.5–57.3)	97.3% (96.6–97.8)	91.6% (90.6–92.5)	78.9% (74.7–82.5)	40.7 (31.2–53.0)
+ Absolute change (1 h, ≥5 ng/L) (n = 242/417, 58%)	38.2% (34.2–42.4)	98.9% (98.5–99.2)	90.4% (89.4–91.3)	85.5% (80.6–89.4)	55.7 (38.3–81.1)
+ Absolute change (2 h, ≥10 ng/L) (n = 160/417, 38%)	29.2% (25.2–33.5)	99.2% (98.8–99.5)	90.6% (89.6–91.5)	84.4% (78.0–89.2)	52.0 (33.4–80.8)
+ Absolute change (3 h, ≥10 ng/L) (n = 97/417, 23%)	21.3% (17.6–25.6)	99.6% (99.3–99.8)	90.9% (89.9–91.8)	87.6% (79.6–92.8)	70.9 (38.3–131.2)
+ Relative change (1 h, ≥10%) (n = 156/417, 37%)	25.3% (21.8–29.1)	99.4% (99.1–99.6)	88.7% (87.6–89.7)	87.8% (81.8–92.1)	56.5 (34.6–92.2)
+ Relative change (2 h, ≥20%) (n = 101/417, 24%)	19.0% (15.7–22.8)	99.6% (99.3–99.8)	89.4% (88.4–90.4)	87.1% (79.2–92.3)	57.2 (31.6–103.4)
+ Relative change (3 h, ≥20%) (n = 70/417, 17%)	15.8% (12.5–19.7)	99.8% (99.5–99.9)	90.4% (89.3–91.3)	90.0% (80.8–95.1)	84.3 (38.3–185.5)

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Table 2. Performance of different cutoffs of hs-cTnT for prediction of AMI.[a] *(Continued from page 442)*

	Sensitivity (95% CI)	Specificity (95% CI)	NPV[b] (95% CI)	PPV (95% CI)	Diagnostic odds ratio (95% CI)
hs-cTnT baseline >60 ng/L (n = 371)	47.9% (43.8–52.0)	97.6% (97.0–98.2)	90.7% (89.6–91.7)	79.5% (75.0–83.6)	37.9 (28.7–50.1)
+ Absolute change (1 h, ≥5 ng/L) (n = 221/371, 60%)	34.6% (30.5–38.8)	99.0% (98.5–99.4)	89.8% (88.7–90.9)	85.5% (80.1–89.9)	52.1 (35.2–77.1)
+ Absolute change (2 h, ≥10 ng/L) (n = 142/371, 38%)	25.1% (21.2–29.3)	99.3% (98.9–99.6)	89.9% (88.8–90.9)	83.8% (76.6–89.5)	46.0 (29.0–72.9)
+ Absolute change (3 h, ≥10 ng/L) (n = 85/371, 23%)	17.5% (13.9–21.6)	99.6% (99.3–99.9)	90.1% (89.1–91.2)	85.9% (76.6–92.5)	55.7 (29.9–103.6)
+ Relative change (1 h, ≥10%) (n = 136/371, 37%)	21.8% (18.3–25.5)	99.5% (99.1–99.7)	88.1% (87.0–89.2)	87.5% (80.7–92.6)	51.9 (30.9–87.2)
+ Relative change (2 h, ≥20%) (n = 87/371, 23%)	15.8% (12.6–19.4)	99.6% (99.3–99.9)	88.8% (87.7–89.9)	86.2% (77.1–92.7)	49.6 (26.7–92.1)
+ Relative change (3 h, ≥20%) (n = 60/371, 16%)	12.7% (9.6–16.3)	99.8% (99.5–100)	89.6% (88.5–90.7)	88.3% (77.4–95.2)	65.6 (29.5–145.3)
hs-cTnT baseline >80 ng/L (n = 290)	38.8% (34.9–42.8)	98.4% (97.9–98.9)	89.3% (88.2–90.4)	82.4% (77.5–86.7)	39.3 (28.5–54.2)
+ Absolute change (1 h, ≥5 ng/L) (n = 180/290, 62%)	28.3% (24.6–32.3)	99.3% (98.9–99.6)	88.9% (87.7–89.9)	87.2% (81.4–91.8)	54.5 (34.7–85.6)
+ Absolute change (2 h, ≥10 ng/L) (n = 117/290, 40%)	19.7% (16.2–23.5)	99.4% (99.0–99.7)	88.8% (87.7–89.9)	83.8% (75.8–90.0)	41.0 (24.7–67.7)
+ Absolute change (3 h, ≥10 ng/L) (n = 74/290, 26%)	14.1% (11.0–17.7)	99.7% (99.4–99.9)	89.0% (87.9–90.1)	86.5% (76.5–93.4)	51.9 (26.4–101.9)
+ Relative change (1 h, ≥10%) (n = 103/290, 36%)	16.6% (13.6–20.0)	99.7% (99.3–99.9)	87.3% (86.2–88.4)	89.3% (81.6–94.6)	57.6 (30.6–108.6)
+ Relative change (2 h, ≥20%) (n = 68/290, 23%)	11.8% (9.1–15.1)	99.7% (99.4–99.9)	87.9% (86.7–89.0)	86.8% (76.3–93.8)	47.6 (23.4–96.7)
+ Relative change (3 h, ≥20%) (n = 52/290, 18%)	10.1% (7.4–13.3)	99.8% (99.5–100)	88.6% (87.4–89.7)	88.5% (76.5–95.7)	59.5 (25.2–140.2)
hs-cTnT baseline >100 ng/L (n = 234)	32.3% (28.6–36.2)	98.9% (98.4–99.3)	88.4% (87.3–89.5)	85.0% (79.8–89.4)	43.3 (29.8–63.0)
+ Absolute change (1 h, ≥5 ng/L) (n = 154/234, 66%)	24.1% (20.6–27.9)	99.4% (99.1–99.7)	88.1% (87.0–89.2)	88.3% (82.1–93.0)	56.1 (33.9–92.7)
+ Absolute change (2 h, ≥10 ng/L) (n = 101/234, 43%)	16.5% (13.3–20.0)	99.5% (99.1–99.8)	88.1% (86.9–89.2)	84.2% (75.5–90.7)	39.2 (22.7–67.6)
+ Absolute change (3 h, ≥10 ng/L) (n = 61/234, 26%)	11.2% (8.5–14.4)	99.8% (99.5–100)	88.2% (87.0–89.3)	88.5% (77.7–95.3)	57.5 (25.9–127.2)
+ Relative change (1 h, ≥10%) (n = 86/234, 37%)	14.0% (11.2–17.2)	99.8% (99.5–100)	86.8% (85.6–87.9)	91.9% (83.9–96.7)	74.2 (34.0–161.7)
+ Relative change (2 h, ≥20%) (n = 55/234, 24%)	9.3% (6.9–12.2)	99.8% (99.5–100)	87.2% (86.0–88.3)	87.3% (75.5–94.8)	46.8 (21.0–104.0)
+ Relative change (3 h, ≥20%) (n = 44/234, 19%)	8.3% (6.0–11.2)	99.9% (99.6–100)	87.8% (86.7–88.9)	90.9% (78.3–97.5)	72.2 (25.7–202.8)

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Table 2. Performance of different cutoffs of hs-cTnT for prediction of AMI.[a] *(Continued from page 443)*

	Sensitivity (95% CI)	Specificity (95% CI)	NPV[b] (95% CI)	PPV (95% CI)	Diagnostic odds ratio (95% CI)
hs-cTnT baseline >200 ng/L (n = 118)	16.1% (13.2–19.3)	99.4% (99.0–99.7)	86.1% (84.9–87.2)	83.9% (76.0–90.1)	32.2 (19.5–53.1)
+ Absolute change (1 h, ≥5 ng/L) (n = 80/118, 68%)	11.7% (9.2–14.7)	99.7% (99.3–99.9)	86.0% (84.8–87.2)	86.2% (76.7–93.0)	38.6 (20.2–73.5)
+ Absolute change (2 h, ≥10 ng/L) (n = 53/118, 45%)	7.7% (5.5–10.2)	99.7% (99.4–99.9)	86.0% (84.8–87.2)	81.1% (68.0–90.6)	26.5 (13.2–53.0)
+ Absolute change (3 h, ≥10 ng/L) (n = 29/118, 25%)	4.6% (3.0–6.8)	99.9% (99.6–100)	86.1% (84.9–87.2)	86.2% (68.3–96.2)	38.6 (13.3–111.4)
+ Relative change (1 h, ≥10%) (n = 40/118, 34%)	6.0% (4.1–8.2)	99.8% (99.6–100)	85.3% (84.0–86.4)	87.5% (73.1–95.9)	40.5 (15.8–103.9)
+ Relative change (2 h, ≥20%) (n = 21/118, 18%)	3.2% (1.9–5.1)	99.9% (99.7–100)	85.5% (84.3–86.6)	85.7% (63.6–97.0)	35.3 (10.3–120.3)
+ Relative change (3 h, ≥20%) (n = 18/118, 15%)	3.0% (1.6–4.8)	99.9% (99.7–100)	85.9% (84.7–87.0)	88.9% (65.2–98.7)	48.6 (11.1–212.1)
hs-cTnT baseline >400 ng/L (n = 57)	8.0% (5.9–10.4)	99.8% (99.5–99.9)	85.0% (83.7–86.1)	86.0% (74.2–93.8)	34.6 (16.3–73.5)
+ Absolute change (1 h, ≥5 ng/L) (n = 39/57, 68%)	5.8% (4.0–8.0)	99.9% (99.6–100)	84.9% (83.7–86.1)	89.7% (75.7–97.2)	49.3 (17.4–139.2)
+ Absolute change (2 h, ≥10 ng/L) (n = 25/57, 44%)	3.6% (2.2–5.4)	99.9% (99.6–100)	84.9% (83.7–86.1)	84.0% (63.9–95.5)	29.6 (10.1–86.5)
+ Absolute change (3 h, ≥10 ng/L) (n = 16/57, 28%)	2.2% (1.1–3.9)	99.9% (99.7–100)	85.0% (83.7–86.1)	81.2% (54.3–96.0)	24.5 (6.9–86.3)
+ Relative change (1 h, ≥10%) (n = 19/57, 33%)	3.0% (1.7–4.7)	100% (99.8–100)	84.6% (83.3–85.7)	94.7% (73.9–99.9)	98.5 (13.1–739.4)
+ Relative change (2 h, ≥20%) (n = 9/57, 16%)	1.5% (0.6–2.9)	100% (99.8–100)	84.7% (83.4–85.8)	100% (55.4–100)	NA
+ Relative change (3 h, ≥20%) (n = 8/57, 14%)	1.2% (0.4–2.5)	100% (99.8–100)	84.8% (83.6–86.0)	87.5% (47.3–99.7)	39.2 (4.8–319.0)

[a] Diagnostic performance of different cutoffs of hs-cTnT (Elecsys) at presentation alone and in combination with relative and absolute changes within 1 h, 2 h, and 3 h after presentation. Absolute changes were assay-specific, and relative changes were defined as a change in cardiac troponin concentrations of 10% within 1 h or 20% within 2 h or 3 h.
[b] NPV, negative predictive value; NA, not available.

Table 3. Assay-specific cutoff concentrations to achieve predefined PPVs.

	Number of patients (%)
hs-cTnT Elecsys	
Cutoff >30 ng/L for PPV of about ≥70%	641 (17%)
Cutoff > 52 ng/L for PPV of about ≥75%	417 (11%)
hs-cTnI Architect	
Cutoff >100 ng/L for PPV of about ≥70%	411 (12%)
Cutoff >300 ng/L for PPV of about ≥75%	246 (7%)
hs-cTnI Vista	
Cutoff >100 ng/L for PPV of about ≥70%	245 (13%)
Cutoff >200 ng/L for PPV of about ≥75%	177 (9%)
hs-cTnI Beckman Coulter	
Cutoff >40 ng/L for PPV of about ≥70%	178 (16%)
Cutoff >80 ng/L for PPV of about ≥75%	138 (13%)
s-cTnI Ultra	
Cutoff >60 ng/L for PPV of about ≥70%	415 (15%)
Cutoff > 80 ng/L for PPV of about ≥75%	364 (14%)

tion of 60 ng/L, but not for higher concentrations (Fig. 2A). The addition of absolute and relative 1-h changes to hs-cTnT concentrations at presentation >14 ng/L substantially increased and nearly doubled PPVs from 46.5% (95% CI, 43.6–49.4) to 82.3% (95% CI, 78.0–86.1) and 71.8% (95% CI, 66.8–76.4; both $P < 0.001$), respectively. Adding absolute and relative 2-h and 3-h changes also increased PPVs significantly (all $P < 0.001$). In patients with hs-cTnT concentrations at presentation >30 ng/L [PPV, 69.4% (95% CI, 65.6–73.0)] or >52 ng/L [PPV, 78.9% (95% CI, 74.7–82.5)], the addition of absolute 1-h changes resulted in significantly higher PPVs of 84.7% (95% CI, 80.1–88.6; $P < 0.001$) and 85.5% (95% CI, 80.6–89.4; $P = 0.03$), respectively. Similar results were found for the addition of relative 1-h changes to hs-cTnT concentrations at presentation >30 ng/L and >52 ng/L with resulting PPVs of 85.8% (95% CI, 80.6–90.2; $P < 0.001$) and 87.8% (95% CI, 81.8–92.1; $P = 0.01$), respectively.

In patients with hs-cTnT concentrations at presentation ≥60 ng/L, neither the addition of early absolute nor relative changes significantly improved the resulting PPVs compared with PPVs provided by hs-cTnT concentrations at presentation alone. Similar findings emerged using the other 4 (h)s-cTnI assays and when using the secondary adjudication (Fig. 2B; see also Figs. 2–4 and Tables 10–13 in the online Data Supplement).

DIAGNOSTIC PERFORMANCE OF DIFFERENT hs-cTnT CONCENTRATIONS AT PRESENTATION IN PATIENTS WITH TYPE 1 MYOCARDIAL INFARCTION

The resulting PPVs for prediction of type 1 myocardial infarction were slightly lower compared with PPVs for the composite of type 1 and type 2 myocardial infarction. PPVs increased from 40.6% (95% CI, 37.8–43.4) for hs-cTnT >14 ng/L to 71.2% (95% CI, 66.7–75.4) for >52 ng/L ($P < 0.001$), whereas PPVs in higher hs-cTnT strata remained largely unchanged [e.g., 75.9% (95% CI, 70.6–80.4) for hs-cTnT >80 ng/L vs 78.8% (95% CI, 70.6–85.2) for hs-cTnT >200 ng/L ($P = 0.52$)].

DIAGNOSTIC PERFORMANCE OF DIFFERENT hs-cTnT CONCENTRATIONS AT PRESENTATION IN COMBINATION WITH SIGNS OF MYOCARDIAL ISCHEMIA ON THE ECG

The presence of an ischemic ECG (ST-depression and/or T-wave inversion) in addition to hs-cTnT concentrations further increased the PPVs for prediction of AMI [e.g., 46.5% (95% CI, 43.6–49.4) for hs-cTnT >14 ng/L without ECG changes vs 58.3% (95% CI, 53.6–63.0) for hs-cTnT >14 ng/L with ECG changes; 78.9% (95% CI, 74.7–82.5) for hs-cTnT >52 ng/L without ECG changes vs 84.2% (95% CI, 78.4–88.7) for hs-cTnT >52 ng/L with ECG changes]. However, the addition of an ischemic ECG significantly reduced the number of patients eligible for rule-in of AMI (e.g., 1193 patients with hs-cTnT >14 ng/L without ECG changes vs 420 patients with hs-cTnT >14 ng/L and ECG changes).

PATIENTS WITH HIGHLY INCREASED hs-cTnT CONCENTRATIONS AT PRESENTATION BUT FINAL DIAGNOSES OTHER THAN AMI

Among patients with highly increased hs-cTnT concentrations at presentation but final diagnosis other than AMI, the vast majority had cardiac, but not coronary, disease such as hypertensive crisis, myocarditis, heart failure, tachyarrhythmias, and takotsubo cardiomyopathy (see Table 14 in the online Data Supplement).

Discussion

This large multicenter study was performed to determine the cTn concentrations necessary to achieve a PPV of ≥75% for AMI to justify immediate admission to a monitored unit and, in general, early coronary angiography. We report 6 major findings.

First, increasing strata of (h)s-cTn concentrations were associated with increasing probability of AMI. Second, depending on the hs-cTnT/I assay used, 7% to 14% of patients had cTnT/I concentrations associated with a PPV of ≥75%. Third, the necessary cTn concentration to achieve a PPV of ≥75% was highly variable among 5 hs-cTnT/I assays, and in general at least twice as high for

the hs-cTnI assays compared with the corresponding hs-cTnT concentration. Fourth, the addition of absolute and relative 1-h, 2-h, and 3-h changes significantly increased PPVs only in patients with mild hs-cTnT/I increases at presentation, e.g., up to 60 ng/L for hs-cTnT, but not in patients with even higher concentrations. Fifth, our findings were confirmed using a secondary adjudication including serial measurements of hs-cTnI (Architect) rather than hs-cTnT (Elecsys). This at least in part overcomes the inherent bias when using 1 specific hs-cTn for final adjudication. Sixth, the findings were comparable in patients with type 1 myocardial infarction, and PPVs could be improved further by addition of an ischemic ECG.

Our findings corroborate and extend previous work on the optimization of the early and accurate rule-in of AMI *(14–16, 23, 25, 26)*. The introduction of hs-cTn assays increased diagnostic accuracy for AMI at presentation by their higher sensitivity, which allowed the detection of low-risk patients for early rule-out of AMI *(6, 7, 10, 13, 16, 23, 27, 28)*. However, because of the higher sensitivity and the frequent detection of increased cTn concentrations in patients with conditions other than AMI, clinical specificity for AMI at the 99th percentile decreased substantially. Thus, for physicians the accurate rule-in of AMI has become more challenging owing to a wider range of other diagnoses with increased cTn concentrations to be considered. The extent of training and continuous medical education needed for emergencymedicinespecialists,cardiologists,andinternalmedicine specialists to appropriately interpret hs-cTn concentrations has been largely underestimated *(1–3)*.

To facilitate the rule-in of AMI, the additional use of absolute or relative changes in addition to cTn concentrations at presentation has become the recommended strategy *(9, 29–34)*. The findings of this study provide further support for this strategy, with the clear exception of patients presenting with cTn concentrations 3 to 5 times the 99th percentiles, as the resulting PPVs could not further be improved by the addition of early changes.

The ability to achieve a high enough PPV with a single blood draw is expected to substantially reduce the time needed for the management decisions associated with the triage toward rule-in of AMI including admission to a monitored unit and, in general, early coronary angiography *(1–3)*. The vast majority of patients triaged toward rule-in with a diagnosis other than AMI such as myocarditis, takotsubo cardiomyopathy, and acute heart failure will still require treatment in a monitored unit. Similarly, most patients triaged toward rule-in with a diagnosis other than AMI may still require coronary angiography for reliable diagnosis. The acceleration and simplification of patient pathways by decision-making based on a highly increased cTn concentration obtained from a single blood draw may be associated with improved medical and economic outcomes *(1–3)*.

It is important to highlight that serial sampling for cTn until the peak cTn concentration has been reached should still remain the standard of care, as it is an accepted method of estimating infarct size *(1–3)*. However, waiting for the results of serial sampling should not cause a delay in the management decision necessary early in the ED.

Our study has several important strengths. First, our study is a multicenter study with nearly 4000 patients. Therefore, this analysis has appropriate power to detect clinically meaningful differences in PPVs between different strategies. Second, we used a strong methodology for the adjudication of the final diagnosis including all available medical records obtained during clinical care, cardiac imaging, serial clinical (h)s-cTn concentrations, as well as study-specific assessments including serial hs-cTnT (primary adjudication) or hs-cTnI (secondary adjudication) blood concentrations obtained from study samples and follow-up evaluations. Third, we examined several (h)s-cTn assays to maximize the generalizability of findings.

It is important to highlight that all strategies for rule-in of AMI should always be used in conjunction with all other information available to the clinicians including vital signs, the 12-lead ECG, and chest pain characteristics *(2)*. Therefore, PPVs for rule-in may increase when combining cTn concentrations with ECG changes or specific chest pain characteristics.

Some limitations merit consideration when interpreting these findings. First, our study was conducted in ED patients with symptoms suggestive of AMI. Further studies are required to quantify the utility of single cTn concentrations to predict AMI in patients with either a higher pretest probability (e.g., in a coronary care unit setting) or a lower pretest probability (e.g., in a general practitioner setting) for AMI. Second, no specific sample size calculation was performed. Although this secondary analysis from an ongoing multicenter study is 1 of the largest ever performed, it still may have been underpowered for some comparisons. Third, we did not adjust for multiple testing. To minimize the risk of false-positive findings, we have prioritized the analysis for hs-cTnT, as this was the assay with the most data available in our study. Fourth, not all patients with acute chest pain had laboratory measurements at 1 h, 2 h, and 3 h. The most common reasons for missing blood samples were logistics issues in the ED, early transfer to the catheter laboratory or coronary care unit, and diagnostic procedures that precluded blood draws. However, it is unlikely that the absence of these patients meaningfully influenced our results. Fifth, although we used a strong methodology to adjudicate the presence or absence of AMI including central adjudication by experienced cardiologists and serial

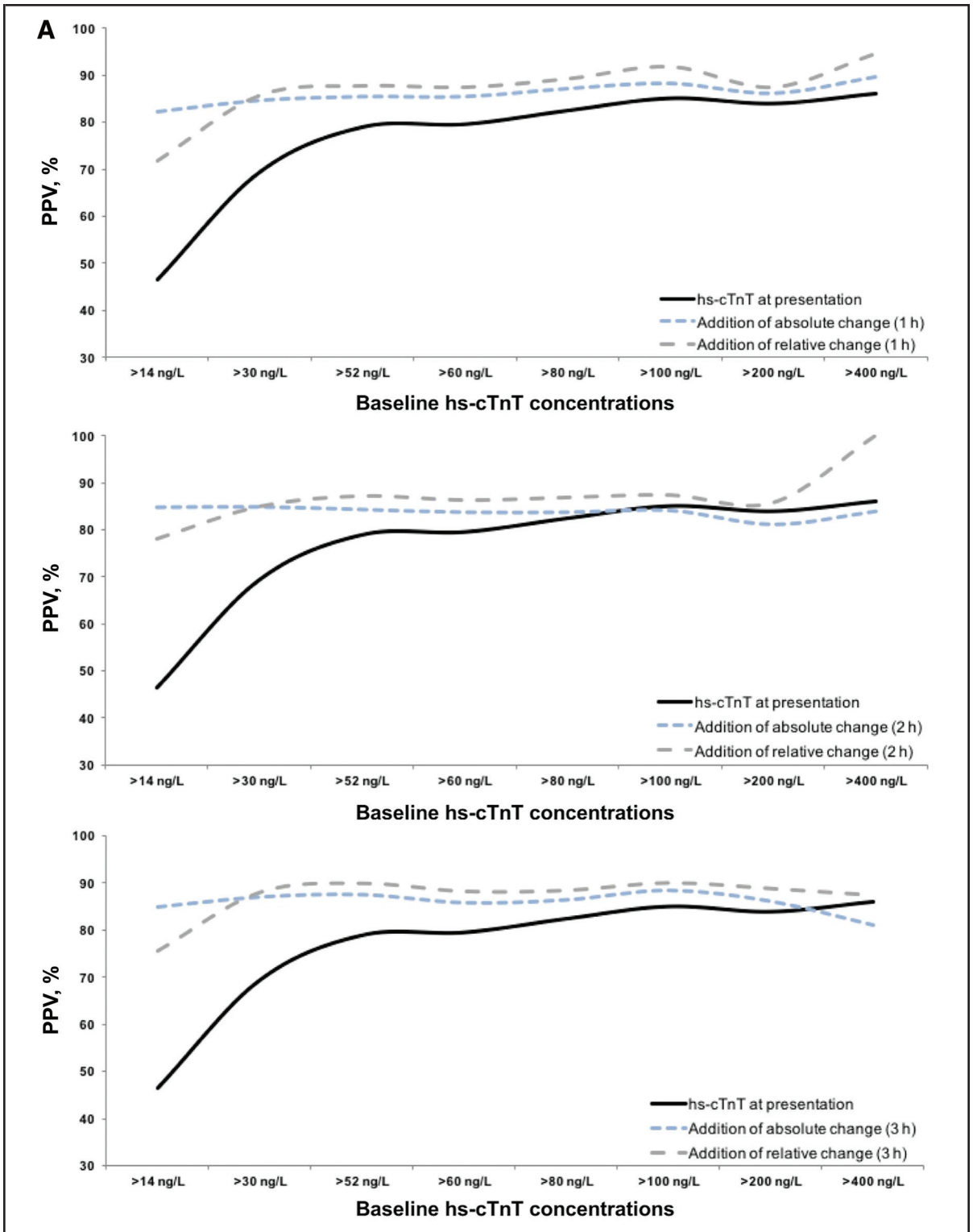

Fig. 2. PPVs for AMI of hs-cTn concentrations at presentation alone and in combination with absolute and relative changes.
(A), hs-cTnT concentrations at presentation alone and in combination with relative and absolute changes within 1 h, 2 h, and 3 h. (B), hs-cTnI (Architect) concentrations at presentation alone and in combination with relative and absolute changes within 1 h, 2 h, and 3 h.

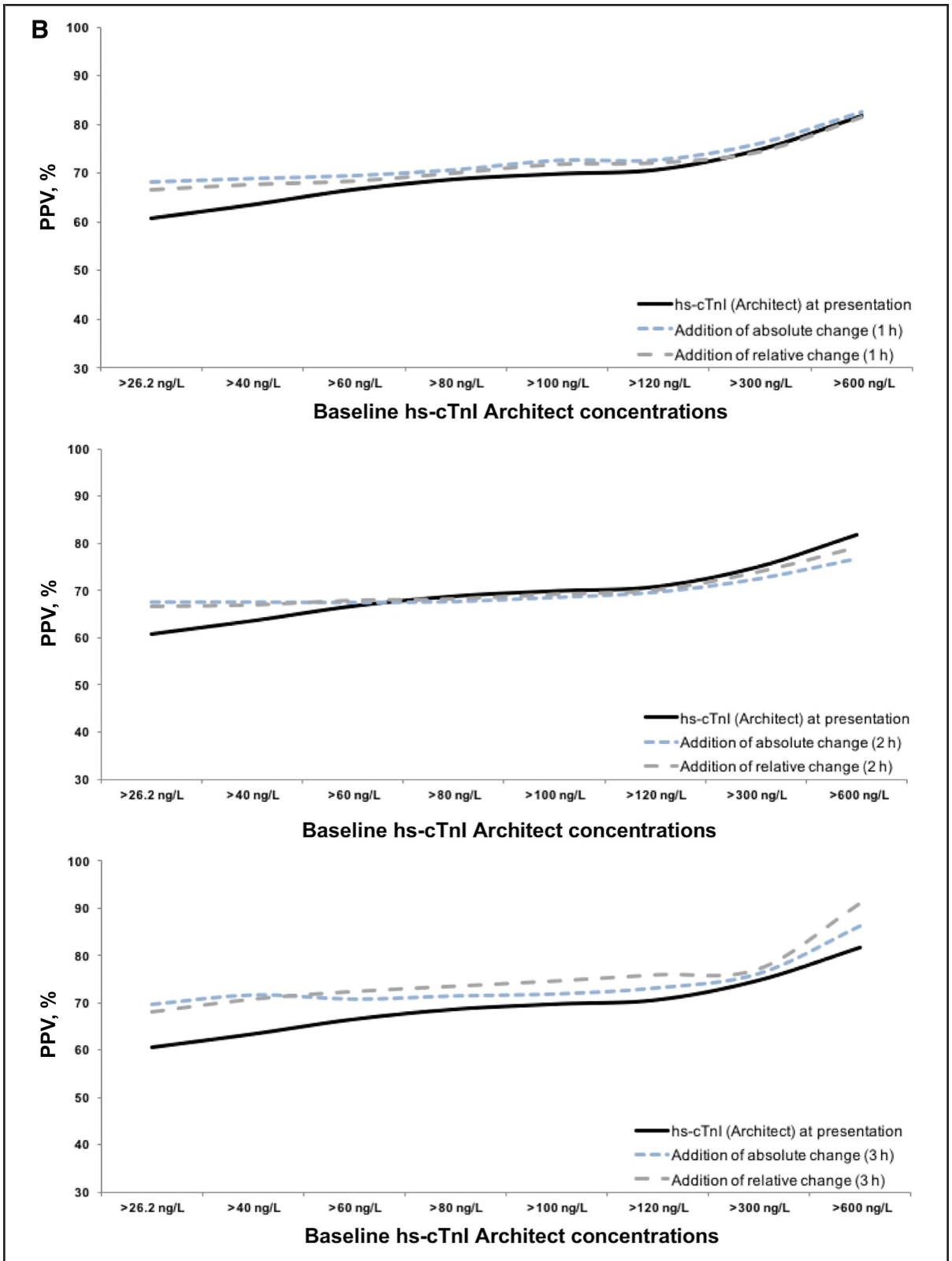

Fig. 2–*Continued*

measurements of hs-cTn, we still may have misclassified a small number of patients. Sixth, our findings are specific to the investigated (h)s-cTn assays. Three of the 5 assays are not clinically available (e.g., the Beckman Coulter assay is an experimental prototype). Before possible clinical use, thresholds should be externally validated. Once other assays become available, additional studies will be needed to examine whether our findings can be generalized to those assays. Seventh, we cannot generalize our findings to patients with terminal kidney failure requiring dialysis because they were excluded from this study. Eighth, there is no universal consensus on what PPV is sufficient in an individual patient to proceed with immediate admission to a monitored unit and/or early coronary angiography. Although the specific threshold predefined for this analysis (75%) is in agreement with current guideline recommendations, the finding of a lack of further improvement in PPV with serial sampling is not affected by the PPV threshold used.

In conclusion, serial sampling does not seem necessary for rule-in of AMI and concurrent decision-making in about 10% of patients with suspected AMI at presentation, as it only marginally increases the PPV for AMI and not in a statistically or clinically significant way. The respective hs-cTnT/I concentration achieving a high-enough PPV for immediate triage toward rule-in is assay-dependent and highly variable. Physicians need to familiarize themselves in detail with the hs-cTnT/I assay(s) used at their institution to best be able to apply these assays.

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